REMARKS

Status of the Claims

Claims 1-9 and 13-25 are currently pending in the application. Claims 1-9 and 12 stand rejected. Claim 7 has been amended. Claim 12 has been cancelled. All amendments and cancellations of claims are made without prejudice or disclaimer. No new matter has been added by way of the present amendments. Specifically, the amendment to claim 7 is supported by the specification at, for instance, page 5, lines 10-11, and pages 8-10, and by the knowledge of one of ordinary skill in the art, who knows and understanding what is generally meant by the term "homology." Reconsideration is respectfully requested.

Further, it is noted that the Examiner's Office Action Summary does not reflect the correct number of claims pending. The Office Action appears to not take into consideration the Supplemental Amendment filed on July 17, 2007 which provides entry of new claims 13-25. Thus, claims 1-9 and 12-25 are actually pending in the present application. However, the status of claims 13-25 are unknown since the Examiner has not considered these claims in the Office Action of July 30, 2007. Therefore, entry and consideration of the July 17, 2007 Supplemental Amendment is respectfully requested.

Amendments to the Specification

Enclosed herewith in full compliance with 37 C.F.R. §§1.821-1.825 is a Substitute Sequence Listing to be inserted into the specification as indicated above. The Substitute Sequence Listing in no way introduces new matter into the specification. Also submitted herewith in full compliance with 37 C.F.R. §§1.821-1.825 is a disk copy of the Substitute

Sequence Listing. The disk copy of the Sequence Listing, file "2005-11-01 1254-0274PUS1.ST25.txt", is identical to the paper copy, except that it lacks formatting.

The Substitute Sequence listing is submitted to correct a typographical error in SEQ ID NO:6. That is, SEQ ID NO:6 recites Val-Leu-Leu at amino acid positions 10-12. This is incorrect. The correct amino acids at positions 10-12 of SEQ ID NO:6 should be Leu-Leu-Val. This typographical error is clearly evident from the proper amino acid sequence disclosed at Figure 1, which discloses Leu-Leu-Val at positions 10-12 of SEQ ID NO:6, the *mus musculus* sequence of GPC3.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 7-9 and 12 stand rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. (*See*, Office Action of July 30, 2007, at page 2, hereinafter, "Office Action"). Claim 12 has been cancelled herein without prejudice or disclaimer, thus obviating the rejection of claim 12. Applicants traverse the rejection as to the remaining claims as set forth herein.

The Examiner states that claim 7 does not provide a reference sequence from which to compare sequence homology. (*Id.*).

Although Applicants do not agree that claim 7 is indefinite, to expedite prosecution, claim 7 has been amended herein to replace the term "antigen" with "native protein" and to replace the term "homology" with the phrase "sequence identity."

Applicants again insist that claim 7 is in fact definite to one of skill in the art. It is clear that claim 7 encompasses a process of producing an antibody by immunizing a nonhuman animal

with a human protein which is highly homologous based on protein sequence identity to a protein native to the nonhuman animal being immunized. That is, the protein which serves as the antigen is a human protein, and this protein has a sequence which is 94% or more identical to a homologous protein found in the nonhuman animal's genome. Further, it is clear to one of skill in the art that the nonhuman animal have a Fas function defect.

As support for the indefiniteness rejection, the Examiner continues to allege that there is a missing reference sequence in claim 7. However, as previously explained by Applicants, no reference sequence is needed or intended in claim 7. That is, all claims need not recite a sequence (SEQ ID NO) simply because the Examiner feels one should be present. The presently claimed invention is clearly directed to immunization of nonhuman animals with human proteins, *any* known human protein, wherein the human protein being used as the antigen has a counterpart nonhuman homolog in the genome of the nonhuman animal. This appears to be entirely clear from the simple language of claim 7. Applicants obviously cannot amend claim 7 to recite the sequence of every known human protein. Such a claim would be dozens of pages long.

Furthermore, Applicants believe claim 7, at least as amended, is definite.

Since no independent reasoning is provided for the rejection of dependent claims 8 and 9, dependent claims 8 and 9 are likewise believed to be definite for, *inter alia*, depending from a definite base claim, claim 7.

Reconsideration and withdrawal of the indefiniteness rejection of claims 7-9 are respectfully requested.

Rejections Under 35 U.S.C. § 102(b)

Claims 7-9 and 12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Paul et al., U.S. Patent No. 6,235,714 (hereinafter referred to as "Paul et al."). (*See*, Office Action, at page 3). Claim 12 has been cancelled herein without prejudice or disclaimer, thus obviating the rejection of claim 12. Applicants traverse the rejection as to the remaining claims as set forth herein.

The Examiner states that the human antigen CRAA-IL1-β peptide is 100% homologous with the mouse peptide antigen and is encompassed by the presently claimed invention. (*Id.*). The Examiner further states that Paul et al. disclose other target antigens listed in Fig. 19 which exhibit high sequence homology between mouse and human proteins. (*Id.*).

Although Applicants do not agree that claim 7 is anticipated by Paul et al., to expedite prosecution, claim 7 has been amended herein without prejudice or disclaimer to recite, "A process for producing an antibody comprising immunizing a nonhuman animal with Fas function defects with a human native protein which has a sequence identity of 94% or more at the amino acid sequence level to a homolog protein of the nonhuman animal to be immunized." As amended, claim 7 is now directed to only those native proteins having an amino acid sequence identity of 94% or greater.

Paul et al. disclose at lines 26 to 35 in the 3rd column, that the CRAA have three essential elements and have the following formula:X1-Y-E-X2. Xl and X2 are peptide sequences containing about 3-10 contiguous amino acids forming an epitope of a target antigen. Y is a basic residue (Arg or Lys). E is an electrophilic reaction center designed to react covalently with nucleophilic side chains of certain amino acids. That is, the invention disclosed in Paul et al. has

as an essential feature the requirement that E must be present adjacent to Y in order to obtain antibodies.

In contrast, the antigen used for the claimed inventions of claims 7 to 9 is characterized in that the homology between the antigen derived from nonhuman animal and the homolog antigen thereof of a human is high (94% sequence identity). Accordingly, the claimed inventions of claims 7 to 9 of the present application are different from the invention of Paul et al. in these essential features. The presently claimed invention does not require the specific formula required by the invention of Paul et al.

In the method of the presently claimed invention, a soluble protein is used to immunize a nonhuman animal. That is, a protein which is expressed on a membrane of a cell is solubilized to be used, as Examples of the present application describe, and a protein which is secreted as a soluble form can be used as it because it is already soluble.

In Paul et al., a mouse is immunized with an antigen expressing cell as disclosed in column 14. That is, the method of Paul et al. can be applied for only insoluble antigens.

Among the proteins listed in Figs 19A and 19B of Paul et al., macrophage inhibitory factor, TNFα, Complement Component C5, IL-1β, clotting factor VII, IL-4, IL-5, IgE, eotaxin and PDGF are liquid (soluble) factors. As to these liquid factors, it is impossible to produce an antibody since these liquid factors are secreted in a culture medium and are not bound to the surface of a cell. Accordingly, these liquid factors are not disclosed in Paul et al. such that an antibody can be produced. That is, Paul et al. does not provide an enabling disclosure of the presently claimed invention.

"The single reference must describe and enable the claimed invention, including all claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention." (*See*, *Elan Pharmaceuticals Inc. v. Mayo Foundation for Medical Education and Research*, 64 U.S.P.Q.2d 1292, 1296 (Fed. Cir. 2002), citing *Crown Operations International, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1375, 62 U.S.P.Q.2d 1917, 1921 (Fed. Cir. 2002); and *In re Spada*, 911 F.2d 705, 708, 15 U.S.P.Q.2d 1655, 1657 (Fed. Cir. 1990), stating "the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it").

Among the proteins listed in Figs 19A and 19B of Paul et al. are CD4, HER2, EGFR, CD8O, CD86, CD28, CD70, CD11b, CD18, CD23, ICAM-1, VLA-4 Integrin Receptor, IL-1β Receptor, GPIIb/IIIa Receptor, PAI-1, IL-4 Receptor, IL-5 Receptor, eotaxin Receptor, PDGF β Receptor and alpha.v.beta3.

Integrins are membrane binding proteins. These proteins do not have sequence identity of 94% or more as illustrated in Exhibit A, which is enclosed herewith. Exhibit A shows the result of the sequence identity search of the membrane binding protein in Figs 19A and 19B between a human and a mouse. There are no proteins disclosed in either of Figures 19A or 19B having a sequence identity which is more than 94%. Accordingly, these proteins are not encompassed by a human native protein which has sequence identity of 94% or more, as presently claimed in amended claim 7.

Dependent claims 8 and 9 are not anticipated as, *inter alia*, depending from a non-anticipated base claim, claim 7.

Reconsideration and withdrawal of the anticipation rejection of claims 7-9 and 12 are respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

Kayagaki et al. & Fu et al.

Claims 7-9 and 12 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kayagaki et al., EP 0872488 (hereinafter referred to as "Kayagaki et al.") in view of Fu et al., *Science* 297:2006-2008, 2002 (hereinafter, "Fu et al."). (*See*, Office Action, at page 4). Claim 12 has been cancelled herein without prejudice or disclaimer, thus obviating the rejection of claim 12. Applicants traverse the rejection as to the remaining claims as set forth herein.

Applicants submitted a verified English language translation of the priority document PCT/JP02/08998 in the reply of July 17, 2007. Thus, the effective filing date of the presently claimed invention of September 4, 2002 predates the publication date of Fu et al. (September 20, 2002). Thus, Fu et al. is not available as prior art, thereby obviating the present rejection. The pending claims of the present application are supported by the priority document as follows: claims 1 to 6 are correspondent to claims 1 to 6 of PCT/P02/08998; and claims 7 to 9 are supported by claims 7 to 10 of PCT/JP02/08998.

Kayagaki et al., Fu et al. & Veugelers et al.

Claims 1-5 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kayagaki et al. in view of Fu et al., and further in view of Veugelers et al., *J. Biol. Chem.*, 274(38):26968-

26977, 1999 (hereinafter, "Veugelers et al."). (*See*, Office Action, at page 5). Applicants traverse the rejection as set forth herein.

Applicants submitted a verified English language translation of the priority document PCT/JP02/08998 in the reply of July 17, 2007. Thus, the effective filing date of the presently claimed invention of September 4, 2002 predates the publication date of Fu et al. (September 20, 2002). Thus, Fu et al. is not available as prior art, thereby obviating the present rejection. The pending claims of the present application are supported by the priority document as follows: claims 1 to 6 are correspondent to claims 1 to 6 of PCT/P02/08998; and claims 7 to 9 are supported by claims 7 to 10 of PCT/JP02/08998.

Kayagaki et al., Fu et al. & Veugelers et al.

Claims 1-6 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kayagaki et al. in view of Fu et al., and further in view of Veugelers et al. (*See*, Office Action, at page 4). Applicants traverse the rejection as set forth herein.

Applicants submitted a verified English language translation of the priority document PCT/JP02/08998 in the reply of July 17, 2007. Thus, the effective filing date of the presently claimed invention of September 4, 2002 predates the publication date of Fu et al. (September 20, 2002). Thus, Fu et al. is not available as prior art, thereby obviating the present rejection. The pending claims of the present application are supported by the priority document as follows: claims 1 to 6 are correspondent to claims 1 to 6 of PCT/P02/08998; and claims 7 to 9 are supported by claims 7 to 10 of PCT/JP02/08998.

CONCLUSION

If the Examiner has any questions or comments, please contact Thomas J. Siepmann, Ph.D., Registration No 57,374, at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____ #42874

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Attachments: Exhibit A - Alignment of human and mouse Sequences of Figures 19A and 19B of Paul et al. (29 pages)

Substitute Sequence Listing, paper copy (5 pages) and CRF copy (1 disk)